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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/587,320 | 05/10/2007 | Noriaki Kato | 868_012 | 4731 |

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| EXAMINER | |
|---|---|
| WESTERBERG, NISSA M | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/587,320 | KATO ET AL. | |
| | Examiner | Art Unit | |
| | Nissa M. Westerberg | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12/11/08, 1/9/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *10 - 12, 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 - 12, 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 11, 2008 has been entered.

### *Response to Arguments*

2. Applicant's arguments filed December 11, 2008 have been fully considered. The rejection under 35 USC 103(a) over Akita et al. (Acta Med Okayama 1993) in view of Lopes de Faria (Acta Ophthalmol Scand 1999) is withdrawn. As the same primary reference, Akita et al., is used in the new grounds of rejection presented below, those arguments put forth with Akita et al. that are relevant to the new rejection are addressed.

Applicant has argued that the primary reference, Akita et al., describes a treatment method for diabetic retinopathy and not diabetic maculopathy, as recited in the instant claims. In response to the Examiner's request for more information regarding

the differences between these two conditions, Applicant have pointed to the paragraph bridging pages 1 and 2 of the instant specification, which states "the object of diabetic retinopathy therapy is to prevent blindness (loss of visual acuity), while the object of diabetic maculopathy therapy if to prevent and ameliorate deterioration of visual acuity" (emphasis added). Further, the specification states that clinically problematic deterioration of visual acuity is due to maculopathy, and the treatments such as photocoagulation which are adequate for diabetic retinopathy are not sufficient for diabetic maculopathy and therefore different treatments for the two conditions are required. It is unclear if the sentence on page 2, ln 2 – 4 of "This is also important in light of treatment of not a few patients having maculopathy only without having retinopathy" means that only a few patients have maculopathy without also suffering from retinopathy, or if the number of patients with diabetic maculopathy and not diabetic retinopathy are not few in number and therefore represent a substantial portion of patients.

This does not explain to the Examiner the differences in symptoms and pathophysiology between these two conditions. The desired outcomes of preventing loss of visual acuity and the prevention of deterioration of visual acuity are different ways of phrasing the same outcome. The macula is a specific portion of the retina that is mainly responsible for central vision, and therefore it appears to the Examiner that diabetic maculopathy is the result of diabetic retinopathy affecting the entire retina, including the macula, to such an extent that clinically problematic changes in vision are experienced by the patient. This finding would be counteracted by evidence indicating

that patients suffering from diabetic maculopathy do not or have not suffered from diabetic retinopathy.

Applicant has argued that Akita et al. establish the utility of the material in experimental tests in animals, but there is no evidence in that reference that any treatment or indeed any success in clinical treatment using that compound in the treatment of diabetic retinopathy. To date, no results have shown the successful use of SNK-860 for the treatment of SNK-860, and several references have been cited as showing that this compound was not effective for the treatment of diabetic retinopathy. The results presented in that Rule 1.132 Declaration, submitted July 16, 2008 by Noriaki Kato, indicates that only two members of the class of aldose reductase inhibitors (ARIs), SNK-860 and epalrestat, are capable of giving positive effects in diabetic retinopathy, and of these, SNK-860 was much more effective. The experimental conditions described in the declaration were chosen such that the model animals had a macula lutae was present. Macula lutae are found in primates, but not in rats. As the experiments presented in the specification in rats (which lack a macula lutae) showed potency of SNK-860 has potency on retinal (macular) function leading to visual acuity, while a monkey model of diabetic maculopathy were also done by forming diffuse macular edemas, the same type of condition as in the rats. Therefore, this unexpected in the art results are clearly established and the rejection should be withdrawn.

The primary reference indicates that the administration of SNK-860 to rats prevents physiological changes which are associated with retinal damage in rats. The instant specification indicates that experiments in diabetic monkeys confirmed that the

edema expressing model in a rat is suitable for the evaluation of diabetic maculopathy (p 4, ¶ 2). This statement from the specification appears to contradict the statements made by Applicant that the lack of a macula lutae in rats could indicate that the model in which macula lutae is present is required for a strong indication of potential success of a treatment. The purpose of animal models is to carry out studies that would take too long and/or would be too costly to carry out in humans.

Various references are presented to document that ARIs have not shown consistent results in clinical trials against the treatment of DR. In addition to the points made by Applicant in their response, the Examiner wishes to point out the Speicher, also in the first paragraph on p 242, further states that while the clinical studies for ARIs have not shown consistent benefits, but it appears that the study design was not optimal. Because of that factor and the compelling nature of the outcomes observed for these compounds in animal models and the effects observed in cell culture, interest in the class of ARIs will remain high. Akita et al. presents compelling evidence regarding the efficacy of SNK-860 in an animal model of ocular complications from diabetes.

A prima facie case of obviousness does not require an absolute certainty that a particular compound will work for the treatment of a particular condition. Rather a reasonable expectation of success in the mind of one of ordinary skill in the art is sufficient. As one of ordinary skill in the field would know, success of a compound in treating a model condition in an animal does not provide absolute certainty that the compound will work in a human having the actual condition, the fundamental premise of

drug research and development is that there is an expectation that the compound will work in a human.

***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10 – 12 and 14 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Mylari (US 6,426,341).

Mylari disclose the treatment of diabetic complications such as diabetic retinopathy by the administration of a composition comprising an aldose reductase inhibitor (ARI; abstract). ARIs function in human and other animals to prevent or reduce the accumulation of unwanted galactitol in various diabetic subjects (col 1, ln 20 – 28. A preferred ARI is fidarestat (col 2, ln 25 – 26), a compound that is also known by the names (2S, 4S)-6-fluoro-2',5'-dioxospiro [chroman-4,4'-imidazolidine]-2-carboxamide and SNK-860.

Mylari discloses the administration of an ARI such as SNK-860 to diabetic patients. The claims of the instant application require the active step of SNK-860 administration. As the active steps are the same, the effect of the administration of

SNK-860 must be the same, namely the treatment of diabetic maculopathy. Applicant has indicated that the "object of diabetic maculopathy therapy if to prevent and ameliorate deterioration of visual acuity" (p 1 of the instant specification, last paragraph). Where selection of one named species from a list of alternatives is all that is required to arrive at the instantly claimed subject matter, that species is anticipated. *Ex Parte A.*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). See also *In re Sivaramakrishnan*, 213 USPQ 441 (CCPA 1982).

A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The reference is believed to be anticipatory as discussed above. For the sake of completeness of prosecution, purely *arguendo* and with regard to this particular ground of rejection only, however, it will be presumed that the prior art differs from the instant claims insofar as it does not explicitly disclose the administration of composition comprising SNK-860 to a diabetic human. If that is so, it would have been obvious to one of ordinary skill in the art to administer a dosage form comprising SNK-860 to a human diabetic patient. As discussed above, the administration of the SNK-860 dosage form will result in the limitations in the preamble of the claim being met.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 10 – 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akita et al. (Acta Med Okayama) in view of Wani et al. (JK Practitioner 2003).

Akita et al. discloses the use of SNK-980, the compound of claim 12, as an aldose reductase inhibitor for the treatment of histopathological changes in retinal tissues (p 299, col 1 – col 2). In a diabetic rat model, SNK-860 was administered orally (p 300, col 1, paragraph 2). Diabetic rats that were not administered SNK-860 developed pathological folding of the retina with retinal edema or cell dissociation that was not seen in non-diabetic rats or diabetic rats given SNK-860 (p 300, col 2, paragraph 5). Leakage of albumin from the blood vessels in the area under these folds of diabetic rats not receiving SNK-860 was also observed (p 302, col 2, paragraph 2).

Akita et al. does not explicitly indicate that the retinal changes in the rat model of diabetes as being diffuse macular edema in diabetic maculopathy.

Wani et al. disclose that diabetic retinopathy can cause blindness in both the proliferative and background stages of the disease. In the background stages of diabetic retinopathy, the visual impairment is caused by the direct involvement of the macular area, a condition to which the term maculopathy is often applied (p 276, col 2, ¶ 1). "The maculopathy is invariably associated with other changes of either proliferative or proliferative diabetic retinopathy Diabetic maculopathy has varied clinical manifestations and presents differently in different patients. Patients with early diabetic retinopathy are usually asymptomatic and the fundus changes are usually not clinically apparent before 5 years of systemic disease" (p 277, col 2, ¶ 2). It is the development of edema,

exudates, etc. that leads to patients complaining of visual symptoms (p 277, col 2, ¶ 2), at which time when they were likely to go to a doctor for diagnosis. Depending on the predominant clinical features, maculopathy can be divided into types such a focal, diffuse and ischemic but there is often overlap between these categories and many reports do not distinguish between the various forms but only discuss macular edema, the first and dominant sign of maculopathy (p 277, col 2, ¶ 3).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer SNK-860 to a human diabetic patient in order to treat the pathological manifestation of diabetes in the eye, such as diffuse macular edema of diabetic maculopathy. The person of ordinary skill in the art would have been motivated and reasonably would have expected success because Akita et al. discloses that SNK-860 inhibits the physiological change associated with widely used rat model of diabetes and Wani et al. discloses that the conditions diabetic retinopathy and diabetic maculopathy are intimately linked. The various classifications of maculopathy, such as diffuse maculopathy, do not have one accepted definition in the field and there is overlap in the patient populations for each "subtype" of maculopathy, if the forms are distinguished from each other.

Given the overlap in patient populations and the varied clinical manifestations of diabetic retinopathy and diabetic maculopathy, one of ordinary skill in the art would treat diabetic patients suffering from visual symptoms and dysfunctions with SNK-860, including the subset of patients suffering from diffuse macular edema in diabetic maculopathy, as SNK-860 has shown activity in limiting the physiological changes to the

retina in a diabetic rat model. Additionally, Applicant has indicated that "the object of diabetic maculopathy therapy if to prevent and ameliorate deterioration of visual acuity" (p 1 of the instant specification). By inhibiting the physiological changes which occur in the retinas in diabetic subjects which are not treated with SNK-860, the administration of SNK-860 will ameliorate the deterioration of visual acuity, which is the object of the intended therapeutic method.

## ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW